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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/657,738	09/08/2003	Jotham W. Coe	PC25077A	8936

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/657,738	COE ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *9,11-13 and 17-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,14-16 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01262004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-28 are pending in this application.

Election/Restrictions

Applicant's election with traverse of Group II, claims 1-8, 10, 14-16 and 25-28, drawn to compounds of formula I wherein m = 1 and n = 2, in the reply filed on November 14, 2005 is acknowledged. The traversal is on the ground(s) that the restriction is improper because there is no undue burden to examine all the groups. This is not found persuasive because the compounds of Groups I-VI are structurally dissimilar and are not art recognized equivalents. They are structurally dissimilar such that a reference anticipating a compound of Group I may not render the compounds of Groups II-VI obvious or vice-versa. 37 CFR 1.141(a) provides that two or more independent and distinct inventions may not be claimed in one application, whether or not the misjoinder occurred in one claim or more than one claim. Restriction is going to be exercised where independent and distinct inventions are presented in one Markush grouping. Independent means when the compound is being made and/or used alone, not in combination with other compounds of the Markush expression. Furthermore, applicant did not submit evidence or identify such evidence now of record showing that the compounds of Groups I-VI are obvious variants or clearly admit on the record that this is the case. Restriction is considered proper in Markush claims where the members are so diverse and unrelated that a prior art reference anticipating the claim with respect to one of the members, would not render the claims obvious under 35 U.S.C. 103 with respect to the other members. Therefore, what should be considered for patentable distinctness is the compound as a whole. Each of the groups are

classified separately (as shown by the distinct class/subclass in the restriction requirement of the previous office action) and further, the compounds of Groups I-VI require separate searches in the literature and therefore, it is burdensome for the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's election of the species of 4-(5-Trifluoromethyl-pyridin-3-yl)-1,4-diazabicyclo[3.2.1]octane is acknowledged. As the elected species was not found in the prior art, the search was expanded to the elected invention of Group II.

Claims 9, 11-13 and 17-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention(s), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 14, 2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition for treating anxiety; or a method of treating anxiety, does not reasonably provide enablement for a pharmaceutical composition for treating **all** disorders or conditions recited in claims 25-26; or a method of treating **all** disorders or conditions recited in claims 27-28. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant composition claims recite a particular intended use for the composition, i.e., for treatment of a disorder or condition selected from a wide list of disorders. The specification, however, does not provide enablement for all of the listed disorders based on the effectiveness of the compounds in binding to neuronal nicotinic acetylcholine specific receptor sites and therefore, useful in modulating cholinergic function. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

The specification fails to enable one skilled in the art to use the instantly claimed compounds or composition thereof. The use disclosed in the specification is on the effectiveness of the compounds in binding to neuronal nicotinic acetylcholine specific receptor sites and

therefore, useful in modulating cholinergic function and thus, useful to treat a variety of diseases, see specification pages 19-22. Biological assays to test the activity of the compounds are provided on pages 40-42, and it is concluded that the compounds of the invention bind to nicotinic receptors. However, the specification does not provide how this binding activity links to the treatment of all types of disorders and there is no reasonable basis for assuming that the myriad of compounds embraced by the instant claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art (directed to nicotinic receptor binding agents) for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also, see MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally an unpredictable and highly structure specific area.

The scope of the claims is not adequately enabled solely based on the activity related to nicotinic receptor binding activity provided in the specification. The claim language includes diseases that are known and those that are yet to be discovered, for which there is no enablement. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as pharmaceutical therapeutic agents that bind to neuronal nicotinic acetylcholine specific receptor sites, useful to treat the laundry list of diseases, which include inflammatory bowel disease, ulcerative colitis, ... Crohn's disease, ... chronic pain, ... ALS, ... , senile dementia, ... AIDS, ... Chemical dependencies and addictions on or to nicotine, tobacco products, ... psychosis, etc. Test assays and procedures are provided in the specification at pages 40-42, and

it is concluded that the compounds of the invention exhibited IC_{50} values showing their binding activity to nicotinic receptors, however, there is nothing in the disclosure regarding how this data correlates to the treatment of the diverse disorders of the instant claims. The disorders encompassed by the instant claims include neurodegenerative diseases, etc., some of which have been proven to be extremely difficult to treat. Regarding the pharmacology of a nicotinic agonist, a state of the art reference, Damaj et al. (Medline abstract enclosed) expresses that "additional pharmacological studies are needed to establish its selectivity at multiple nicotinic receptors", see the abstract. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, the instant claims includes a variety of conditions which fall within the meaning of "neurodegenerative diseases", see the claims reciting disorders such as disease-induced cognitive impairment arising from Alzheimer's disease, senile dementia, ... Parkinson's disease, multiple sclerosis, ALS, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). For example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease." (pg. 1994).

The instant claim includes 'a method of treating chemical dependencies and addictions' - the scope of which is beyond what has been established for such a treating effect. The specification teaches that the compounds exhibit nicotinic receptor binding activity. However, the notion that a compound could be effective against addiction in general is absolutely contrary to the current understanding of addiction generally. Although the term "addiction" implies a single entity, in fact it is a complex and variable network of services tailored to meet the multiple needs of the individual. There is not, and probably never will be, a pharmacological treatment for 'addiction' generally. That is because it is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Abuse of the use of barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc. all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Abusive use of heroin, for example, arises from binding at the opiate receptors, cigarette addiction arises from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find a pharmaceutical to treat drug abuse generally have thus failed. Because addiction has so many dimensions and disrupts so many aspects of an individual's life, treatment for this illness is never simple.

The instant claim includes 'a method of treating Alzheimer's disease, impulsivity, anxiety, stress, depression, schizophrenia, cognitive disorders, Parkinson's, movement disorders, sleep-wake cycle, incentive motivation, etc.', however, applicant has not provided any correlation between nicotinic receptor binding activity and the instantly claimed therapeutic method. Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat

effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease" (pg. 1994). It is known that antipsychotic medications are used to reduce the psychotic symptoms of schizophrenia. The state of the art of such antipsychotic drugs, however, indicates that 'they do not cure or restrain the symptoms of schizophrenia or ensure that there will be no further psychotic episodes'. The online information about the treatment options of the disease http://www.psychologyinfo.com/schizophrenia/medication-treatment.html indicates that 'it is difficult to predict which patients will benefit from treatment with antipsychotic drugs. Different patients have different treatment responses and side effects to various antipsychotic drugs', thus, clearly indicating the unpredictability in the dosage regimen.

The instant claims include 'a method of treating ulcers' - "ulcers" are non-healing wounds that develop on the skin, mucous membranes or eye. Peptic ulcers, for example, are treated with antacids or H2 antagonists. A state of the art reference, Sonis, provides that "Despite its clinical and economic consequences, there is no approved therapy for mucositis. ..... A key challenge to the development of any therapy that is aimed at modulating radiation- or chemotherapy-associated toxicity is to ensure that it targets normal tissue effectively, but does not diminish the tumoricidal impact of the antineoplastic treatment" (see the enclosed article).

The instant claim recites diseases such as sleep disorders, jet lag, etc. for which applicant does not provide any nexus between these diseases and the disclosed nicotinic binding activity of the compounds. The instant claims recite 'a method of treating AIDS'. Marcus et al. (see the enclosed PubMed Abstract), in their recent publication expressed that 'despite advances, the

global spread of HIV and especially its spread in developing countries continues almost unabated'. Also, van Heeswijk et al., (PubMed Abstract enclosed) stated that, "further clinical studies are needed to identify optimal combinations for treatment of antiretroviral naïve and experienced HIV-1 infected patients". Despite the unprecedented successes in the therapy of HIV infection, AIDS remains a major world health problem being the first cause of death in Africa and the fourth leading cause of death worldwide. Despite the success of protease and reverse transcriptase inhibitors, new drugs to suppress HIV-1 replication are still needed. Thus it is clear from the above evidence that the ability to treat diseases associated with HIV is highly unpredictable and has met with very little success.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Recent studies on experimental and clinical pharmacology of nicotinic acetylcholine receptors cited in Annual Reports in Medicinal Chemistry indicate that the following disorders may be associated with nicotinic acetylcholine receptors: senile dementia of the Alzheimer's type, Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesias, mania, depression, attention deficit disorder, anxiety, dyslexia, schizophrenia, Tourette's syndrome and smoking cessation. The "nicotinic" effect with respect to Alzheimer's is hypothesized. Parkinson's Disease is "presently of unknown etiology" and recent studies have exhibited dosing

problems as well as "unusually high placebo effects". The pathophysiology of Tourette's syndrome is unknown. Additionally, there are other pathological non-CNS conditions, such as pouchitis and influenza virus-induced pneuomonitis, where nicotinic efficacy has been reported, but remains to be confirmed.

Recent review of nicotinic receptor suggests the use of these ligands still under experimental stage. See Mirza et al., Psychopharmacology 148(3) : 243-250, 2000, Terry et al., Neuroscience 10192) : 357-368, 2000 and Court et al., J. Chem. Neuroanat. 20(3-4) : 281-298, 2000 (PubMed Abstracts provided). It is difficult to treat many of the disorders claimed herein. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of *in vivo* efficacy by those skilled in the art. See for example *In re Ruskin* 148 USPQ 221; *Ex parte Jovanovics* 211 USPQ 907. Applicant has not provided any reference(s) that forms sufficient evidence that claimed uses were art-recognized based on activity relied on at the time of applicants' effective filing date. MPEP 2164.05(a). When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and

complications, which is essential to establish the dosage regimen for appropriate treatment. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or inhibition of the claimed disorders, nor indicate competent technical references in the appropriate methods.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements). This clearly highlights the unpredictability in the art and the need for undue experimentation. Furthermore, there is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders encompassed by the instant claims.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10, 14-16 and 25-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 1, it is recited that "A compound.... **and** all enantiomeric, diastereomeric, and tautomeric isomers **and** pharmaceutically acceptable salts thereof", which is unclear because it is not clear if 'a compound or a salt thereof' is claimed **or** 'a **mixture** of a compound and the salt' is claimed. Replacing with -- A compound..... ~~and all~~ or an enantiomeric, diastereomeric, and tautomeric ~~isomers~~ isomer thereof or a pharmaceutically acceptable ~~salts~~ salt thereof -- would overcome the rejection.
2. In claims 25-28, the recitation "epilepsy, **including** petit mal absence epilepsy" is confusing. The phrase "including" renders the claim indefinite because it is unclear whether the limitation following the phrase is part of the claimed invention.

Claim Rejections - 35 USC § 102

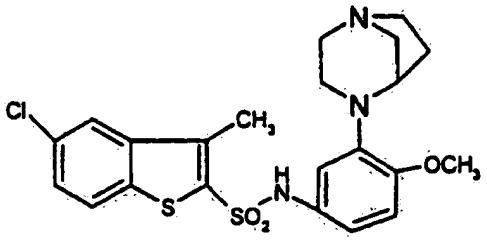
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 10, and 25-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Bromidge et al., WO 99/42465. The instant claims read on reference disclosed compounds, see the compounds of formula (I) in page 1 and the corresponding species of Example 5 (depicted below for convenience):

Example 5

5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(1,4-diazabicyclo-[3.2.1]oct-4-yl)-4-methoxyphenyl]amide (E5)



Receipt is acknowledged of the Information Disclosure Statement filed on January 26, 2004 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

January 22, 2006